Effect of High Intensity Interval Training on Blood Glucose Control in Experimental Animal of Type 2 Diabetes Mellitus：A systematic review and meta-analysis

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Abstract: **Objective** To explore the effect of high intensity interval training (HIIT) on blood glucose control in experimental animal of type 2 diabetes mellitus (T2DM) and to evaluate the quality of the included studies. **Methods** literatures were obtained by searching PubMed, EMbase, Web of Science, BIOSIS Preview and Cochrane Library. Chinese literatures were obtained through CNKI, WanFang Data, SinoMed and VIP Database; The collection and screening studies were conducted in strict accordance with inclusion/exclusion criteria. The methodological quality and reporting quality of the included studies were evaluated using SYRCLE's risk of bias tool for animal studies (SYRCLE) and Animal Research: Reporting In Vivo Experiments guidelines 2.0(ARRIVE2.0). Outcomes， such as body weight (BW), fasting blood glucose (FBG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA) were meta-analyzed and evaluated by Grading of Recommendations Assessment, Development and Evaluation (GRADE). **Results** Twenty studies were included, including male mice (9) or rats (11). T2DM models have been developed mainly in two ways: high-fat diet and/or combined with streptozotocin (STZ) injection (15 articles), genetic modification (5 articles). Exercise and interval intensity are measured using $VO_{2\ max}$, maximum speed and slope, with 1-4.5 minutes of exercise and 15 second -3 minutes of interval, and the training duration was 8-13 weeks with 3-5 times of training a week. The SYRCLE's result was mainly uncertain； None of the single items or the single studies assessed by ARRIVE 2.0 appeared complete. Standardized mean difference (SMD) combined the effect size of outcomes showed that compared with the sedentary control group, the heterogeneity was all large, and there are significant differences in FBG, HOMA. Very low quality of all evidence assessed by GRADE. **Conclusions** The effect of HIIT on blood glucose control is clear, but the influencing factors are complex, the risk of bias is high, the quality of reporting is low, the source of heterogeneity in outcomes is complex, and the quality of evidence is extremely low, which make its reliability and validity are questioned. It is recommended to use ARRIVE2.0 as a guide to increase the integrity and transparency of research information and improve research

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quality through experimental protocol registration and attachments.
Key words: Type 2 Diabetes Mellitus; Experimental Animals; High-intensity Interval Training; System Review; Meta Analysis

Type 2 Diabetes Mellitus (T2DM) is a serious metabolic disease, the incidence of which is increasing year by year worldwide. It is an unprecedented and uncontrolled pandemic, with 1 in 4 diabetic patients worldwide originating from China[1].The incidence of diabetes is still increasing in China, the prevalence of diabetes in people aged 18 years and older increased from 10.4% in 2013 to 11.2% in 2017[2]. High-intensity Interval Training (HIIT) is a current popular sports and exercise concept and method. As of 2021, HIIT has been ranked in the top five global fitness trends released by the American College of Sports Medicine for 8 consecutive years[3]. HIIT can improve insulin sensitivity in adults, and HIIT may be associated with greater cardiovascular benefits in people at high risk for T2DM[4]. However, in patients with T2DM, by what biological mechanisms does HIIT work, and what is the effect of HIIT on complications and other important outcomes? Are there advantages compared to other exercise interventions? How is the security? Due to the long period and difficulty of clinical experimental research and the possibility of patient accidents, the current research evidence is very limited, and the research conclusions are still unclear[5]. Animal experiments are a good alternative research strategy, and many researchers have tried to use animal experiments to explain the above problems. It's just that HIIT, as an exercise training intervention, has a broad and holistic effect on the organism, and the effect is slow and reversible compared to drugs. There are many and complex influencing factors in the experiment, and improper handling will lead to the decline of the research quality and even the wrong conclusions. The methodology and quality of the current animal experiments reporting on HIIT intervention in T2DM, and the characteristics of the research outcomes are the preconditions for determining the value of animal experiments. This study attempts to use the method of Systematic Reviews/Meta-Analysis (SRs/MAs) to summarize the evidence, so as to provide researchers with high-quality evidence-based evidence, optimize experimental protocols, and reduce repeated studies. Maximize the information that is beneficial to human health promotion in animal experimental research, and realize the principle of "Reduce, Replace, and Refine" for experimental animals.

This research protocol is registered in PROSPERO, registration code: CRD42021244120, the report is completed according to the protocol and the actual situation of included studies; The report is based on systematic reviews and Meta-Analyses priority reporting items (PRISMA2020) statement, the full text and abstract are checked against the PRISMA2020 list and abstract list one by one, and the check results are shown in the Supplement of Appendix 1 and 2.

1 Study Subjects and Methods

1.1 Inclusion and Exclusion criteria

Inclusion and exclusion criteria are based on the PICOS principle: participants, interventions,

comparisons, outcomes, study design.

1.1.1 Inclusion criteria

⑴ Study design: experimental study.

⑵ Participants: T2DM animal model, unlimited species of experimental animals.

⑶ Intervention and control protocol: HIIT: exercise intensity is based on> 80-95% VO2max or equivalent peak heart rate (HR peak), equivalent running speed; the specific exercise type, exercise time, interval time, duration, frequency of HIIT was not limited. There was no limit on the control group.

⑷ Outcomes: ①body weight (BW), ②fasting blood glucose (FBG), ③fasting insulin (FINS), ④ HOmeostasis Model Assessment-Insulin Resistance (HOMA).

1.1.2 Exclusion criteria

① repeated search and published literature; ②excluded in vitro studies, cell and tissue culture studies, and human studies; ③Research methods are observational studies, systematic review plans, traditional reviews, systematic reviews/Meta-analysis; ④ Exclude literatures for which the full text cannot be obtained (conference abstracts, etc.); ⑤ Different literatures published in the same study shall be recorded as one study, and the outcomes will not be included repeatedly.

1.2 Strategies for the literature search

PubMed, Embase, Web of Science (WOS), Biosis Preview database (BP), Cochrane Library， CNKI, WanFang, VIP and SinoMed used to obtain literature. The search period was from the establishment of the database to August 23, 2021， and has no year of publication or language restrictions. The supplementary search strategy adopted the retrieval of relevant systematic reviews/meta-analyses and reference lists of included original studies to obtain more articles that met the inclusion criteria. According to the requirements of PRISMA2020 statement, the search formula and search results of each database have been provided, in Appendix 3 and the document package.

1.3 Literature screening and data extraction

Literature screening and data extraction were completed independently by two researchers and summarized by a third researcher. If the results were inconsistent, a consensus was formed through three-person discussion.

1.3.1 Literature screening: First, obtained literatures were imported into the Endnote software, Duplicate literatures were excluded by Find Duplicates combined with researchers' manual comparison and checking; Then read the titles and abstracts to exclude the literatures that do not meet the inclusion criteria, exclude SRs/MAs or other review literatures, and original study literature and conference literature for human or non-animal, non-T2DM; Find and collect full text of literature that may be included in the study, and if the web search lacks data, contact the author by email to supplement it;

Two researchers read the full text independently, checked the exclusion criteria, and screened each

literature one by one. For multiple literatures with repeated research design and study results, one study was reserved, and it was calculated as one study. Literature with no required outcomes were excluded.

1.3.2 Data extraction: First, try to extract the data directly from the text, table and graph. If the required data were reported as graphs, the data has been extracted from the graph using the GetData Graph Digitizer software. Data were extracted from the included studies and placed in data extraction tables. The table includes (1) basic information table: the first author and publication time of the study, country, animal species, ethical registration, fund support, outcomes and comments; (2) Experimental design scheme table: experimental animal information and T2DM induction method; strain, number, week age, gender, weight, temperature, humidity, sunshine, etc. Drug and method of administration, concentration, dose, site, number, and success criterion, Sample size of the intervention group; (3) Interventions and comparison measures table: exercise type, intensity, time, interval exercise type, interval exercise intensity, interval exercise time, repetition number, frequency, program duration span and control measures, were extracted successively; The outcomes of this study were all continuous variables, including BW (g), FBG (mmol / L), FINS (mmol / L) and HOMA. After data extraction, if unreported or unclear data was found, and an attempt will be made to contact the author by email (up to two attempts).

1.4 Quality assessment of the included studies

1.4.1 The risk of research bias was assessed using the SYRCLE (Systematic Review Centre for Laboratory animal Experimentation) tool for assessing risk of bias in animal experiments[6]. As Appendix 4, the SYRCLE tool includes six aspects: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other. There are 10 items include sequence generation, baseline characteristics, allocation concealment, random housing, blinding, randomized outcome assessment, blinding, incomplete outcome reporting, selective outcome reporting, and other sources of bias. "Yes", "No" and "Unclear" judgments are made, and finally expressed as a percentage.

1.4.2 The reporting quality of the included studies was assessed using the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines. The content and principle of the evaluation of animal experimental research reports are based on the ARRIVE 2.0 version updated by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) in July 2020[7].The ARRIVE 2.0 Executive Questionnaire provided by NC3Rs in March 2021, Appendix 5. Strictly follow the key items in ARRIVE2.0 to complete the report quality evaluation of the included studies, and finally obtain the percentage of report completeness according to the answers, perform horizontal comparison of each item in the questionnaire, and obtain a comparison of the answers to individual questions.

1.5. Statistics and Meta-analysis

Meta-analysis was performed statistically by using Stata 16.0 software and Review Manager5.4, all outcomes were expressed by mean±standard deviation (mean±SD), if the original study data

were expressed as mean±standard error (mean±SEM), the formula SD=SEM x $\sqrt{n}$ would be used to convert. The effect size was pooled using the standardized mean difference (SMD), and the effect scale was 95% confidence interval (95% CI). Heterogeneity test (Q test, test level is a=0.1) was used, $I^2 \leq 50\%$, choose fixed effect model for Meta analysis, $I^2 > 50\%$, choose random effect model for Meta analysis, and Sensitivity analysis for its heterogeneity sources, such as subgroup analysis, univariate Meta regression analysis; The following study characteristics will be used as potential sources of heterogeneity: species, modeling and exercise protocol, etc. When $P < 0.05$, the results of the Meta-analysis are statistically significant.

1.6 Evaluation of evidence quality

Evidence quality for outcomes were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[8]. Two researchers independently used the GRADEpro GDT online tool to rate the quality of evidence for the outcomes included in the SR from five aspects: study limitations, publication bias, imprecision, inconsistency, and indirectness[9], Cross-check after completion, and any dispute shall be decided by the study instructor.

2 Results

2.1 Literature search and screening

A total of 446 articles were obtained from the first search, including 35 Chinese articles and 411 English articles, imported into Endnote software, checked the author, journal name, publication time and title one by one, and eliminated 96 duplicate documents; According to the exclusion criteria , the title, abstract were read and articles were removed as follows ①review studies, ②studies with human, ③researches on other animal models, such as obesity, heart failure, etc., ④conference abstracts, if the conference abstracts are studies on HIIT intervention in animal models of T2DM. The full text was obtained through other search methods or emails, and 321 articles were excluded; The full text of the remaining 29 articles was finally obtained, of which 8 were in Chinese and 21 in foreign languages. One study in Korean was translated and read after translation by WPS Kingsoft and Youdao. The research of ESMAEILI S2018[34] is in Persian, and the information is obtained by reading the English title, abstract, key words and combining with the professional Persian translation provided by Huiquan Translation Company. Detailed literature screening flow and results are shown in Appendix 6.

2.2 Data extraction of the included study

2.2.1 Basic information of the inclusion and exclusion of studies

The basic information of the 29 papers included in the full-text reading is shown in Table 1. There are 12 studies in which the experimental animals were mice, and the strains were all C57BL. There are 17 studies on rats, including 13 studies on Wistar, 3 articles on SD, and 1 article on OLETF; Eighteen papers were approved by the ethics committee, and eight were supported by funds. From the first author, there are 12 papers from China, including 7 mice and 5 rats; 11 papers from Iran are all rats;3 in Norway, 1 in France, 1 in the United States, and 1 in South

Korea. Except for a study in the United States, which was in rats, the rest were all in mice; In the process of reading the full text, according to the basic situation of the research data, the experimental design and the outcome indicators, it is judged whether different literatures are the same study. The criteria are as follows: outcomes of the two studies are exactly the same, or outcomes are partially the same and the intervention plan is the same. If multiple studies are the same study, keep the literature with the most outcomes to be included, followed by keep journal papers or keep updated literature. ESMAEILI S2018[34], Amri, J2019[31], Mohammad P2019[30] have the same intervention plan and some research results, Amri, J2019[31] with the most outcomes were retained. ZHENG L2020[14] and Zheng Lifang 2021[15], keep journal papers; Kalaki-Jouybari F2020[24] and KHAKDAN S2020[25], Xing Xiaorui2019[32] and Li Xun2018[33]， Zhang, Q2020[12] and Zhang Qiang2017[17] are all the same studies, keep an updated research; Lin Sen2020[23] and Zhang Xiaofei2020[22] are the same study, and the exercise program used is before the induction of diabetes, which is not in line with this study; ROLIM N2015[20] did not meet the inclusion criteria and was excluded; 20 papers were finally included in this SRs/MAs.

2.2.2 The experimental design of the included studies

The study design of the 20 included studies is shown in Table 2. All of them are group-controlled experimental studies. Generally, temperature, humidity, and sunshine are introduced, but no details are provided. In terms of inducing T2DM, 4 included studies were db/db mice and 1 was OLETF rats. KHAKDAN S2020[25] was fed with a simple high-fat high-fructose diet (HFHFD); SABOURI M2020[26] and Amri, J2019[31] adopted streptozotocin (STZ) alone; the other 12 studies used high-fat diet combined with STZ. STZ were administered by intraperitoneal injection, and all but one study were administered by one injection; However, the timing and dose of STZ injection are different. Zhang, Q2020[12] reported STZ injection followed by high-fat diet, and at the latest after 12 weeks of a high-fat diet, STZ injection. The injection concentration of STZ is usually diluted with fresh sodium citrate buffer to pH=4.4-4.5; STZ dose, the mice use two doses of 100ml/kg and 10ml/kg, and the rats use doses of 30-65 ml/kg. The sample size of the study was 6-8 individuals/group. The FBG value was used to judge whether T2DM was formed. The judgment criteria were FBG≥16.7mmol/L, FBG≥13.8 mmol/L, and FBG≥11.1mmol/L. However, neither db/db mice nor OLETF rats were introduced to judge T2DM modeling success criteria.

The sample size of the SABOURI M2020[26] grouping was unclear. The total sample size of YAZDANI F2020[27] was 24; After STZ injection, it was still 24 (8/group), but the body weight data was 10/group, it's obvious contradictions. The authors were consulted by email, but did not get any reply; In the MOGHADDAMI K2018[35], there were errors in the conversion of degrees of freedom and the conversion of blood glucose standards mg/dl and mmol/L.

2.2.3 Measures of the HIIT intervention and control groups in the included studies

As shown in Table 3, all exercise methods included in the study were treadmill exercise, and high-intensity exercise was the same as interval exercise; The speed of high-intensity exercise of mice is 15-26m/min, and the speed of high-intensity exercise in rats is 25-36m/min. Adopt the method of increasing load, increase 1-2 m/min every week. The slopes used were 15°, 20° and 25°. The maximum oxygen uptake (VO2max) is usually specified in the range of 80%-95%. The exercise time is 2-4 minutes. The number of repetitions of high-intensity exercise is 4-13 times. The interval way is mainly low-to-medium-intensity exercise, and the intensity is between 0-75% VO2max. The frequency of training is 3-6 times per week; the control group adopts the methods of sedentary, continuous exercise and moderate-intensity intermittent exercise; The time span of sports training in all included studies was between 8 and 13 weeks, of which 8 weeks were the main, including 15 articles, only one study of Stolen2009[21] was 13 weeks, two studies by Amri, J2019[31], Chavanelle, V2017 [19]were 10 weeks, two studies by MOGHADDAMI K2018[35], Martin, J. S2012[38] were 12 weeks.

2.3 Quality Evaluation

2.3.1 Risk of Bias Assessment

Based on the SYRCLE animal experimental bias risk assessment tool, results as shown in Figure 1, selective bias, implementation bias, measurement bias, loss bias, reporting bias and other bias are all impossible to determine through the paper. There were only 3 papers that could be clearly negative in terms of selection bias and other biases.

2.3.2 Report Quality Evaluation

The report quality of the 20 papers included in the study was evaluated according to the key 10 items of the ARRIVE 2.0 executive questionnaire. The contents included study design, sample size, inclusion and exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental animals, experimental procedures, and results. All entries involved a total of 18 issues; Answer yes or no according to the actual situation of each study; The results were shown in Figure 2, Almost all studies did not report the details of randomization and blinding. The basis for determining the sample size, the size of the effect size and the confidence interval were also not provided. In addition, the determination and statistics of the minimum observation unit in the experimental design were not provided. Whether the data in the method conforms to the statistical assumptions is also an overlooked issue in the paper report. The full reporting rate for all studies was below 80%. however, the evaluation reports of experimental animals and outcomes are relatively complete.

2.4. Main effect of HIIT intervention in T2DM outcomes

2.4.1 Results of Meta-Analysis

As shown in Table4, in addition to the two outcomes of BW and HOMA, which were compared between the HIIT intervention and the exercise control group, were I^2<50% and P>0.1 by the Q test, which showed that there was no strong heterogeneity, and fixed effects could be selected for the study. The I^2 values of the remaining outcomes were greater than 50%, which showed strong heterogeneity, so the random effect model was selected. Meta-analysis results showed that HIIT compared with SED, absolute SMD for FBG, FINS and HOMA were greater than 0.5, and the decrease of FBG and HOMA had a very significant difference (P<0.01). Compared with HIIT and EXE, the absolute SMD effect values of BW, FBG, FINS and HOMA were all median between 0.2 and 0.5, but the confidence intervals of the three outcomes were broad and crossed the invalid zone "0".

2.4.2. sensibility analysis

Comparison of HIIT and SED, as shown in Figure 3, BW, FBG, FINS, and HOMA removed any included studies one by one, and compared with HIIT and EXE group, as shown in Figure 4, FBG and FINS removed any included studies one by one, the combined effect size did not change significantly; Using the RM5.4 software to remove an included study one by one, the overall heterogeneity is still high. The subgroup analysis from the population, modeling method, and exercise training time span did not show obvious heterogeneity.

2.5the results of evidence quality evaluation

GRADE evidence quality results are shown in Table 5, with all included samples, BW, FBG, H OMA, and the evidence quality was extremely low.

3. Discussion

Animal studies on HIIT intervention in T2DM are mainly from China and Iran, especially in recent years, showing obvious regional characteristics. The charm of HIIT lies in its high fitness efficiency and short time-consuming, which meets people's sports and fitness needs in the context of fast-paced life and fragmented time in contemporary life. The update iteration of the economic development model and the increasing competition pressure make people more inclined to choose HIIT. The prevalence of T2DM in China and Iran is relatively high[1], and for T2DM patients, the effect of HIIT on improving blood glucose control is of great significance. Animal experimental research on HIIT intervention in T2DM is a scientific issue with strong application value, but it is necessary to pay attention to the repeated reports of the same study in different ways and the consistency of reports. However, it is necessary to pay attention to the inconsistency caused by repeated reports of the same research in different ways to ensure the reliability of the research.

Rodents are used in animal experimental studies on exercise intervention in chronic diseases[39]. The participates included in this study were rats or mice; Judging from the modeling protocols used in the included studies, there are differences in the selection of animal models, the concentration of STZ, the composition of diet-induced food, the feeding time, and the sequence of STZ injections; Judging from the exercise programs selected in the included studies, the HIIT exercise types all use treadmills, but there are obvious differences in the intensity interval and test method, the duration of the exercise, the way and time of the interval exercise, and the frequency of weekly repetitions.

In particular, the duration of the training has a significant effect on the effect of blood glucose control; BW, FBG, FINS, and HOMA were all indirect substitution outcomes[40].It can only reflect the health status statically, and the results are affected by multiple factors such as measurement time, body condition, index testing methods, and instruments; BW, FBG, and FINS are bidirectional in reflecting the effect of HIIT intervention on blood glucose control in T2DM patients, that is, it is meaningless to judge the health-promoting benefit based on the evaluation of the increase and decrease of a single indicator.

In clinical practice studies, the effect of HIIT on BW in patients with T2DM has shown a small effect size, a two-way feature of decreasing[41] and increasing[42]. Exercise regimens should be more carefully defined to improve the quality of the body of evidence for outcomes. Compared with the sedentary group, HIIT significantly decreased FBG and HOMA, and the effect of HIIT on blood glucose control was clear, but it did not show a significant advantage over other exercise methods. From the perspective of PICOS elements, species differences, model and exercise protocol complex differences, the literature strong heterogeneity between outcomes also show that the included studies are very different. All show diversity and uncertainty, and various factors are

intertwined, making it difficult to judge the source of heterogeneity.

High-quality evidence is the basis for realizing the significance of animal experiments, and low risk of bias is the premise to ensure high-quality evidence; SYRCLE evaluation of all included studies showed no or uncertain, Animal experiments of drug intervention have problems of sequence generation, allocation concealment, blinding, and lack of random result evaluation reports[43];

Exercise intervention studies were either unreported or unclear in sequence generation, allocation concealment, randomization of animal placement, randomized outcome assessment, incomplete data reporting, selective outcome reporting, etc. [44]; Blinding is also largely unreported or unclear.

The reproducibility of experimental animal research has attracted more and more attention, and the key to improving the reproducibility of research lies in the transparency of reporting. In order to facilitate practical application, the international organization NC3Rs revised and promulgated of ARRIVE2.0 in 2020, and designed the questionnaire in layers. The basic requirement part is "Key 10 Items of ARRIVE Execution Questionnaire"[7]. But there is still a problem of incomplete reporting[45]; All included studies did not clearly introduce the method of randomization sequence generation and the treatment of potential confounding factors; Blinding is neglected in animal grouping, intervention and outcomes; Regarding the setting of the sample size, although the included studies clearly stated the number of animals in each group of studies (n=), the design and implementation of the experimental unit were neglected, and the basis or instructions for estimating the sample size were lacking, and underreporting basic information from animal studies[46]. Whether it is from the perspective of a single included study or a single item of the ARRIVE2.0 implementation questionnaire, the report is incomplete. Perhaps the journal articles are limited by the publication space, and there is no evidence of "negative" studies in experimental animal studies[47], only use of male animals[48], the consequences of repeated reports of the same study, etc., make the details of the study not fully presented to the reader, resulting in a very low reproducibility of animal studies, even lower than 25%. Appropriate and detailed Sample size calculations and analysis of effects are necessary[49]. The reproducibility crisis is a huge crisis faced by sports science research, and a reasonable response method must be adopted in research practice to keep up with the progress of other disciplines[50].

4. Conclusion

The effect of HIIT on blood glucose control is clear, but the influencing factors are complex, the risk of bias is high, the quality of reporting is low, the source of heterogeneity in outcomes is complex, and the quality of evidence is extremely low, and the reliability and validity are questioned; It is recommended to use ARRIVE2.0 as a guide to increase the integrity and transparency of research information and improve research quality through experimental protocol registration and attachments.

Conflict of Interest:

None.

Supplementary material:

Appendix 1: PRISMA2020 Checklist

Appendix 2: PRISMA2020 Summary Checklist

Appendix 3: Literature Search Strategy and Document Package

Appendix 4: SYRCLE Animal Experimentation Risk of Bias Assessment Tool

Appendix 5: ARRIVE2.0 Implementation Questionnaire

Appendix 6: Literature Screening Process

Appendix 7: all results of a single study

Appendix 8: Data and other available materials

5. References

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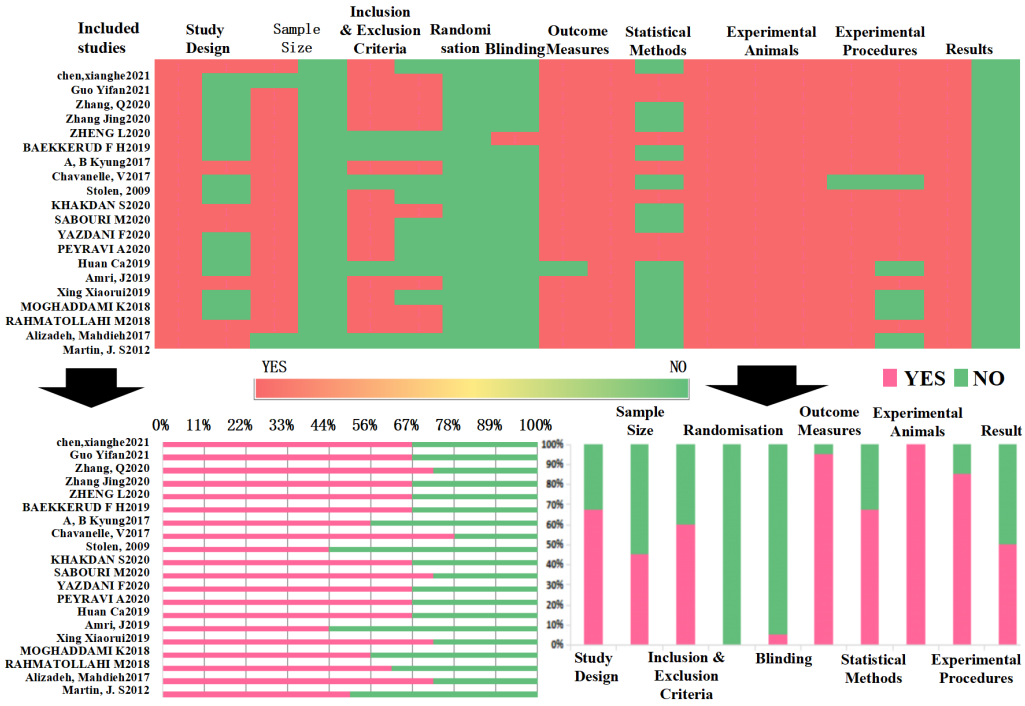

Figure 1 ARRIVE Report quality evaluation diagram

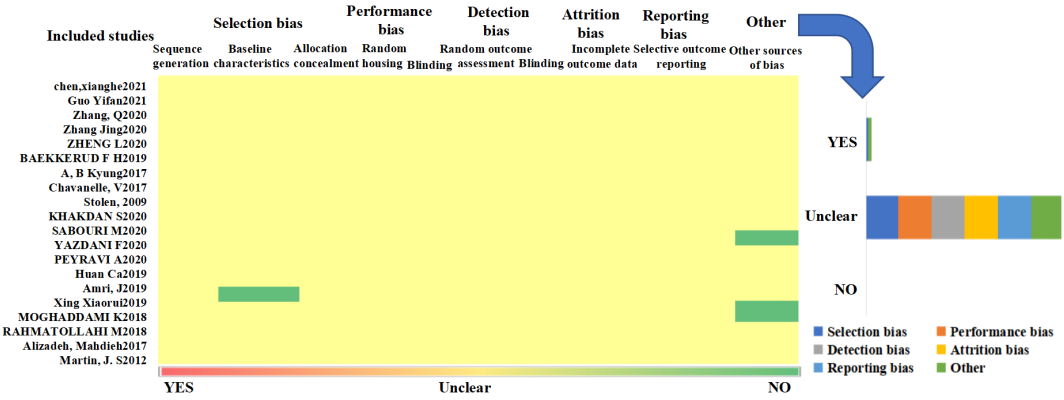

Figure 2 Results of the SYRCLE risk of bias evaluation

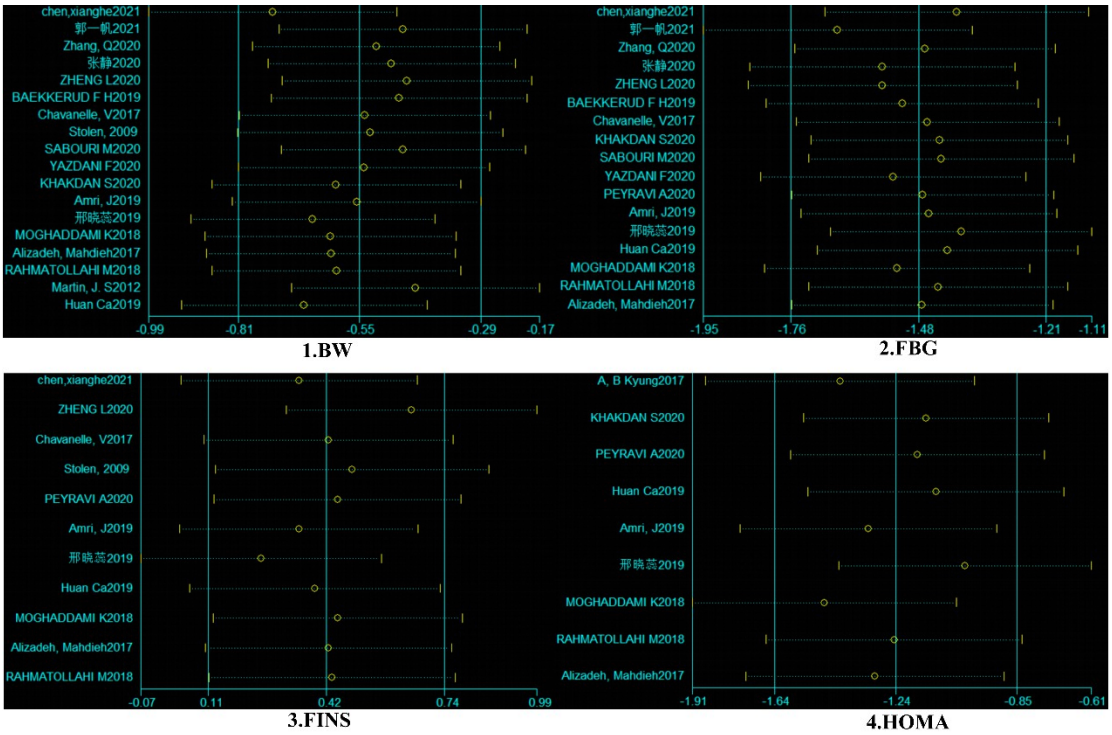

Figure 3 Sensitivity analysis of the comparison between the HIIT intervention and the SED group

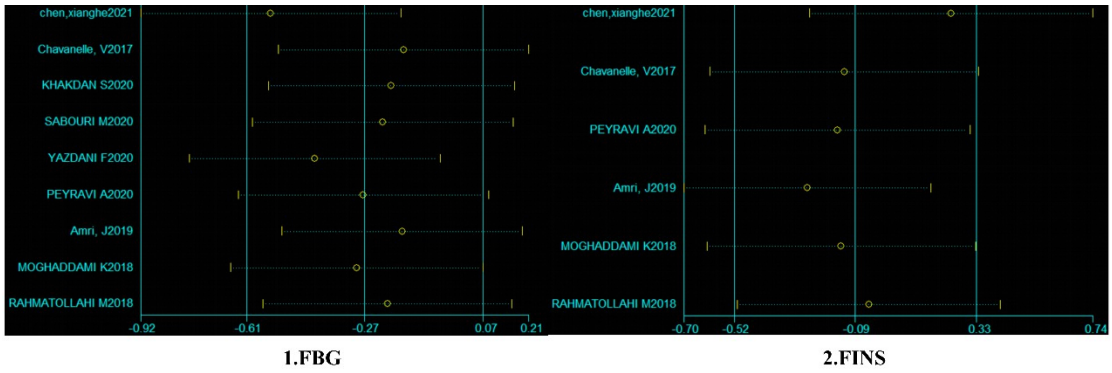

Figure 4 Sensitivity analysis of the comparison between the HIIT intervention and the EXE group

Table 1 Basic information table for inclusion in full-text reading literature

Included studies	country	animal	ethics	fund	outcomes	remarks
Chen, Xianghe2021[10]	China	mice	yes	deny	①②③	
Guo Yifan2021[11]	China	mice	no	no	①②	
Zhang, Q2020[12]	China	mice	yes	yes	①②	same as Zhang Qiang2017
Zhang Jing 2020[13]	China	mice	yes	no	①②③④	
ZHENG L 2020[14]	China	mice	yes	yes	①②③	same as Zheng Lifang2020
Zheng Lifang2020[15]	China	mice	yes	yes	①②③	same as ZHENG L2020 (deletion)
BAEKKERU D F H 2019[16]	Norway	mice	yes	yes	①②	
Zhang Qiang2017[17]	China	mice	no	no	①②③④	same as Zhang, Q2020 (deletion)
A, B Kyung 2017[18]	Korea	mice	no	yes	④	
Chavanelle, V2017[19]	France	mice	yes	no	①②③	
ROLIM N2015[20]	Norway	mice	yes	yes		Myocardial infarction model (deletion)
Stolen, 2009[21]	Norway	mice	yes	no	①③	
Zhang Xiaofei 2020[22]	China	rats	no	no	①②③④	same as Linson 2020 (deleted)
Linson 2020[23]	China	rats	no	no	①②③④	same as Zhang Xiaofei2020 (deletion)
Kalaki-Jouybari F2020[24]	Iran	rats	yes	yes	①②④	same as KHAKDAN S2020 (deletion)
KHAKDAN S 2020[25]	Iran	rats	no	no	①②④	same as Kalaki-Jouybari F2020
SABOURI M 2020[26]	Iran	rats	no	no	①②	
YAZDANI F 2020[27]	Iran	rats	no	no	①②	
PEYRAVI A 2020[28]	Iran	rats	yes	no	②③④	
Huan Ca2019[29]	China	rats	yes	no	①②③④	
Mohammad, P 2019[30]	Iran	rats	yes	yes	①②③	same as Amri, J2019, and ESMAEILI S2018 (deletion)
Amri, J 2019[31]	Iran	rats	yes	no	①②③④	same as Mohammad, P2019 ESMAEILI S2018
Xing Xiaorui 2019[32]	China	rats	no	no	①②③④	same as Li Xun 2018
Li Xun 2018[33]	China	rats	yes	no	①②③④	same as Xing Xiaorui 2019 (deleted)
ESMAEILI S 2018[34]	Iran	rats	yes	no	①②④	same as Mohammad, P2019 Amri, J2019 (deletion)
MOGHADDAMI K 2018[35]	Iran	rats	yes	no	①②③④	
RAHMATOLLAHI M2018[36]	Iran	rats	no	no	①③④	
Alizadeh, Mahdie h 2017[37]	Iran	rats	yes	no	①②③④	
Martin, J.S 2012[38]	America	rats	no	no	①	

Note: ① body weight ② fasting blood glucose ③ fasting insulin ④HOMA

Table 2 Study design of the 20 included studies

	Experimental animal information								The T2DM induction method was performed					
	strain	quantity	weeks of age	sex	weight	temperature	humidity	sunshine	other	Drugs and methods	concentration	dosage	site	number of times	sta ar
e	C57BL/6	52	4	M	/	23±2	55±5	/	1/ cage	Stz was injected after 8 weeks of continuous high-fat dietary feeding.	1%	10	abdomen	3	⩾ .7
	C57BL/6	40	4	M	21.1	21-25	40-50	12/12	/	Stz was injected after 12 weeks of continuous high-fat dietary feeding.	1%	10	abdomen	1	⩾ .7
	C57BL/6J	40	5	M	25.04± 1.98	22±2	40-70	12/12		After Stz administration, mice were fed with HFD.	/	100	abdomen	1	⩾ 11.
	C57BL/6	40	4	M	/	20-25	50-60	12/12	/	Stz was injected after 12 weeks of continuous high-fat dietary feeding.	1%	10	abdomen	1	⩾ 16

	C57BL/6J	/	5	M	21.4±1.6	22±2	40–70	12/12	/	Stz was injected after 12 weeks of continuous high-fat dietary feeding.		100	abdomen	1	> 13
	db/db	47	/	M	/	/	/	12/12	/	animals develop diabetes due to leptin receptor mutations.	/	/	/	/	/
	db/db	30	5	M	20-25 g	20±1	50±10	12/12	/		/	/	/	/	/
	db/db	25?	6	M	/	/	/	/	1/ cage		/	/	/	/	/
	db/db	40	/	M	/	/	/	/	/		/	/	/	/	/
	Wistar rats	30	8	M	200 ± 20 g	18-23	40-60	12/12		High lipid and high glucose alone were induced for 16 weeks.	/	/	/	/	⩾ 11.
	Wistar	40	12	M	220-240	22	45	12/12		Stz injection after 3 weeks of adaptation, and normal diet.	/	50	abdomen	1	⩾ 16
	Wistar	32	12	M	180±20	24±4	50–60	12/12		Stz was injected after 2 weeks of continuous high-fat dietary feeding.	/	35	abdomen	1	> 13.
	SD	56	12	M	150±30	/	/	/	/	Stz injectio	/	30	abdomen	1	⩾

									n after 3 months.					16.
	Wistar	50	8	M	250-280	20-24	/	12/12	/	Stz was injected after 4 weeks of continuous high-fat dietary feeding	/	35	abdomen	1	⩾.1
	Wistar	24	/	M	200-250	25	60	12/12	/	Stz was injected after a week of acclimatization and 12 h of fasting.	/	65	abdomen	1	>13.
	Wistar	40	/	M	160-180	22-26	40-70	natural	1/cage	Stz was injected after 4 weeks of continuous high-fat dietary feeding	/	30	abdomen	1	⩾1.1
5	Wistar	40	8	M	180±20g	/	/	/	/	Stz was injected after 10 weeks of continuous high-fat dietary feeding	/	30	abdomen	1	?≥17
	Wistar	24	6	M	110±10g	22±2	50	12/12		Stz was injected after 8 weeks of continuous high-fat	/	30	abdomen	1	⩾16

										dietary feeding					
n	Wistar	26	5-8	M	110±10g	24±4	50-65	/	3 / cage	Stz was injected after 8 weeks of continuous high-fat dietary feeding	/	30	/	/	⩾16
	OLETF rats	/	4	M	/	/	/	12/12	1/ cage	/	/	/	/	/	/

Note: M: Male; / is unreported; weight unit: g (g); temperature: ° C (℃) Humidity: Relative humidity percentage (%)

T2DM induction method: dose unit: ml / kg, T2DM induction success standard: FBG, mmol / L;

Table 3 Interventions and controls in the included studies

	intervention study.							Control	
	types	intensity	time	type of interval	Interval intensity	interval time	repetitions/time	duration time	
0	treadmill	0° slope, 85%Smax	2	treadmill	45%Smax	3	/	8	1. Sedentary 2. MICT group ran for slope,60%Smax
	treadmill	15°slope, speed 16-26m/min.	4	complete rest	/	2	5	8	Sedentary
	treadmill	25°slope,15-22 m/min 85–90% VO2max	2	treadmill	8 m/min	2	3	8	Sedentary
	treadmill	15°slope, speed 10-26m/min.	4	treadmill	gradually to 0m / min	2	5	8	Sedentary
	treadmill	15°slope, speed 16-26m/min, 85–90% VO2max	4	complete rest	/	2	5	8	Sedentary
H	treadmill	90% VO2max	4	treadmill	70%	2	5	8	Sedentary
	treadmill	0° slope, 80%-	4	treadmill	cooldown 65%-75%	13	3	8	1. Sedentary 2. The low-intensity tra

		90%VO2max			VO2max				speed of 10 m / min fo
	treadmill	20° slope, 85–90 Vmax	4	treadmill	rest	2	5	10	1. Sedentary 2. MICT group ran for 50–60% of Smax
	treadmill	85%- 90% VO2max	4	treadmill	50% of VO2max	2	5	13	Sedentary
	treadmill	85–90% VO2max	2	treadmill	30–40% VO2max	2	5	8	1. Sedentary 2. ran for 60min (15° s 60–65% VO2max)
26	treadmill	90-95% ofVO2max	1	treadmill	50% of VO2 max （20-30 m/min ）	1	5	8	60–65% VO2 max
7	treadmill	0° slope, 90% VO2max	2	treadmill	20-30	1	5	8	1. Sedentary 2. 50–60%VO2max
	treadmill	80%–85% of maximum speed	2	treadmill	active rest periods	1	5	8	1. diabetic control 2.50%–55% maximum of activity extended fr first week to 50 min in
	treadmill	85-95% VO2max	7	treadmill	50-60% VO2max	3	5	8	Sedentary
	treadmill	Odd day 40m /min Even day 54m /min	3min 30s	/	/	/	6	10	1. Sedentary 2.20-60 min, 27m/min
	treadmill	85%~90% VO2max, 25m/min	7	treadmill	15m/min	3min	5	8	Sedentary
	treadmill	85-90% VO2max, speed 25-34m/min,	4	active rest Treadmill	50% VO2max.	2	5	12	1.Sedentary 2MIIT:13 bouts of 4 m intensity running with and 2 minute active res 50% VO2max.16-25 m
I	treadmill	80-85% maximum speed	2	treadmill	/	1	5	8	1. Sedentary 2. low intensity contin
2	treadmill	90% VO2max speed 29-36 m/min,	15-30s	treadmill	/	1	5	8	Sedentary
	treadmill	15%slope, speed 40m/min.	2.5	treadmill	rest	4.5	5	12	1.sedentary 2.For EndEx,60 min o at 20 m/min at a 15%

Note: Smax: maximum speed; Time: minute (min); Duration time: week (w). MICT: moderate intensity continuous training; MIIT: moderate intensity interval training; LIT low-intensity training group; EndEx: Endurance Exercis

Table 4 Meta-analysis results of blood glucose control effects in experimental animals with HIIT

groups	outcomes	Number of included studies	Results of the heterogeneity test		Effect model	Meta analytic result	
			I^2 (%)	P		SMD (95%CI)	P
Comparison of the HIIT intervention with the SED	BW	18	91.6	0.00	random	-0.36（-1.27,0.55）	0.63
	FBG	17	76.1	0.00	random	-1.80（-2.39,-1.21）	0.00
	FINS	11	90.1	0.00	random	1.42（0.35,2.49）	0.16
	HOMA	9	78.5	0.00	random	-1.59（-2.46,-0.72）	0.01
Comparison of the HIIT intervention with the EXE	BW	9	9.8	0.35	fixed	-0.35（-0.67,-0.03）	0.03
	FBG	9	75.2	0.00	random	-0.27（-0.61,0.07）	0.26
	FINS	6	76.4	0.00	random	0.24（-0.67,1.16）	0.63
	HOMA	6	00.0	0.55	fixed	-0.26（-0.69,0.17）	0.23

Table 5 GRADE Quality of Evidence Outcomes for Included Studies

groups	Outcomes	Sample size of the experimental group	Sample size of the control group	Quality of evidence
HIIT VS SED	BW	179	176	Very low
	FBG	154	152	Very low
	FINS	109	106	Very low
	HOMA	73	70	Very low
	FBG	75	76	Very low
	FINS	49	48	Very low
	HOMA	44	44	Very low